Watson (1950) discussed some of the possible explanations for the increased incidence in cancer of the lung. He pointed out that there is an increased awareness on the part of the public and the medical profession, and the prominent symptomatology of cancer of the lung has been well publicized. He observed that the development and use of antibiotics undoubtedly has played an important role in more frequent and more accurate diagnosis of cancer of the lung. In the past, pneumonia in elderly males was a common cause of death, and many of those so-called pneumonias were cases of pneumonitis secondary to bronchogenic cancer. Nevertheless, according to Watson, the death certificate classed the death as one due to pneumonia. Watson estimated that better than 75 percent of the patients now coming to Memorial Hospital, New York, with cancer of the lung, have had a previous clinical diagnosis of virus pneumonia. He concluded that fewer patients die of the inflammatory complications of cancer of the lung in its earlier stages, and therefore many of them now received further clinical study leading to an accurate diagnosis. Watson also called attention to the vastly improved methods of diagnosis now employed in routine chest X-rays studies, and also called attention to the important factor of better cancer teaching at the medical school level.

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Source: https://www.industrydocuments.ucsf.edu/docs/gqbl0000

Wynder (1950) has also called attention to the confusion of virus pneumonia and cancer of the lung, and he has stated that

> "A definite diagnosis of virus pneumonia in a male patient of cancer age and a heavy smoker is a very, very dangerous diagnosis. What does such a diagnosis do? It causes the physician to administer antibiotics without first having made a thorough Roentgenographic study of the chest. Antibiotic treatment almost always gives a patient relief from his cough; the patient may be free of cough for 3 or 4 months, but infrequently, a second administration of penicillin will follow the reappearance of the cough. Six or eight months, then, are past before the physician gets around to making the Roentgenographic, bronchoscopic and microscopic study essential to the correct diagnosis of lung tumor. And why? All because of that diagnosis of virus pneumonia." l.c.

Wynder also believes that as, on the average, about ten months elapse from the time the first symptom appears until the lung cancer receives competent treatment, about one-half of this time lost is caused by incorrect diagnosis by the first physician the patient consults. The other half results from the patient's own negligence.

[redacted]

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Source: https://www.industrydocuments.ucsf.edu/docs/gqbl0000

Doll and Hill (1950) observed that the large and continued increase in the deaths recorded due to lung cancer within the last five years in England and Wales, both in the national figures and in those from teaching hospitals, makes it hard to believe that improved diagnosis can be entirely responsible for the tremendous increase in the incidence of lung cancer. They concluded that there is sufficient reason to reject that factor as the whole explanation of the increase, although no one can deny that it may well have been contributory.

[redacted]

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Source: https://www.industrydocuments.ucsf.edu/docs/gqbl0000

Indent ¶ - Steiner and co-workers (1950 b) contend that their pathologists were just as skilled in recognizing primary lung cancer before the great increase occurred in 1939-43 as they were after that period. They also state that lung cancer presents no greater difficulty in necropsy recognition than do at least two of the control tumors, namely carcinoma of the pancreas and intracranial tumors, and yet these did not show a corresponding increase. Neither do they believe that changing concepts in nomenclature and classification of pleural, mediastinal, and related types of tumor account for the increase. Though they concede that a small part of the increase might be due to a rising total necropsy-permit rate, this and other clinical factors they feel do not explain most of the increase.

[redacted]

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Source: https://www.industrydocuments.ucsf.edu/docs/gqbl0000

Jost (1951), reporting from Germany on pulmonary and bronchial carcinoma, stated. "Autopsy data show that only half of the lung tumors had been diagnosed clinically, whereas today in some clinics and hospitals about 80 to 90% of cases are diagnosed correctly."

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Source: https://www.industrydocuments.ucsf.edu/docs/gqbl0000

INCREASED ATTENTION AS A FACTOR IN LUNG CANCER INCIDENCE:

Some Much of the published material bearing on the influence of improved attention on the reported increase in lung cancer incidence has already been discussed in the preceding section of this chapter ~~entitled "Improved Diagnosis as a Factor in Lung Cancer Incidence"~~, and need not be restated here. Boyd (1939) discussed at length the reasons for the recent increase in the incidence of bronchiogenic carcinoma, and felt that this is not due to some new agent at work in the world, but rather during the last 20 years

knowledge of the disease has been disseminated. He makes the interesting comment:

> "... for more than 400 years it has been known that one of the most common causes of death amongst the miners in Schneeberg in Saxony was the progressing, wasting pulmonary disease, presumed to be tuberculosis or silicosis. In 1922, Schmorl showed by means of a series of autopsies that this mysterious disease was none other than bronchogenic carcinoma. Naturally, there was an immediate tremendous increase in the incidence of that disease as judged by vital statistics, but it had been there since 1500 A.D. waiting to be recognized."

After discussion of the various factors that might account for the increase in lung cancer incidence, Boyd (1939) concluded:

> "Without denying the possibility that there may be some real increase in the incidence of the disease, it was suggested that the various factors which had been discussed, coupled with the present increase in the span of life, was sufficient estimation for the apparent increase which had attracted the attention of observers in all countries - observers, however, who had had their eyes open so that they can look-see as well as look, and to therefore see what they know."

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Source: https://www.industrydocuments.ucsf.edu/docs/gqbl0000

On connection with the factor of diagnosis in lung cancer incidence the following statement by Macklin (1948)

~~Macklin (1948) made the following interesting statement~~

concerning the importance of the "undiagnosed residue" in the statistical incidence of lung cancer is worth citing at length:

> "Nowhere ..... has there been more muddled thinking than on the question of whether lung cancer has increased or not, the question has been impossible to answer because we have no standard of comparison. We have no idea of how many lung cancers were undiagnosed 25 or 15 years ago, and no idea as to how many are undiagnosed today. If 50 percent were not recognized then and only 25 percent were not now, we could feel that lung cancer had increased by 50 percent over what it had been in the past, whereas it has not increased at all, we merely recognized it when we saw it. There is no doubt that it is being diagnosed more frequently, and that the apparent increase is even greater than can be accounted for by increase in age of the population.
>
> "Various methods are resorted to in order to show that lung cancer has increased, even beyond the improvement in diagnosis and increase in age. The percentage of lung cancers in hospital admissions is said to have increased. But the opening of a new pediatric or maternity ward can lower the percentage of cancers in hospital admissions, and the founding of a new surgical unit can increase it. The percentage of lung cancers among necropsies has been thought to be a sounder method of proving the increase .... The zeal with which the physician presses for a necropsy is of prime importance in determining which cases come to necropsy, and the zeal .... is directly proportional to the lack of clarity in the diagnosis. A third method ..... is the estimation of increase of lung cancer cases among the cancer necropsy cases. Breast, uterine, rectal or prostatic cancer can be diagnosed by biopsy or at operation ..... the patient with vague symptoms ..... will come to necropsy, and may prove to be a lung cancer. Thus, since not all cancer cases were necropsied then and now, such increase may be spurious ..... there is not a single criterion by which we can prove that lung cancer is actually affecting more persons in the lung cancer age groups now than it did 25 years ago." (~~underlines~~ not in original) underlining

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Source: https://www.industrydocuments.ucsf.edu/docs/gqbl0000

Klotz (1938) concluded that the increase in the incidence of lung cancer is due in part to the increase in longevity and to the clinical interest stimulated by ~~the~~ X-ray, bronchoscopic examination and biopsy

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techniques and by more consistent recognition of bronchial carcinomas at autopsy. This worker concluded:

> "It would appear ..... that much of the increase in bronchial carcinoma is apparent. How much of the increase is real will probably never be known, the world never having been in the state of a pathologist's Utopia where necropsy routinely follows death."

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Ronser (1950) observed that in spite of the considerable work done on lung cancer in the last 20 years, "we are still far from certain that the increase is real, or that the conditions in which we live are related to the cause of the disease". He commented further;

> "Is not this the time for a small body of active people interested in lung cancer to pool their ideas and plan an investigation which might at some future date provide the facts needed to answer these questions? At present there is no organization for collecting the crucial data either from the victims of the disease or from people who might serve as controls".

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Source: https://www.industrydocuments.ucsf.edu/docs/gqbl0000

Steiner and co-workers (1950 b) observed that the tumors used as controls in their study at the Los Angeles County Hospital did not show the increase exhibited by lung cancer, although there was presumably equally great clinical interest in them. Furthermore, the increase antedated the development of pneumonectomy and lobectomy for therapy of this disease at that hospital, so they do not consider increased attention as a factor in lung cancer increase.

[redacted]

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Source: https://www.industrydocuments.ucsf.edu/docs/gqbl0000

"In a recent review Rigdon and Kirchoff (1952) presented a table giving the deaths and death rates for cancer of the lung, physicians and persons per physician ratio, and hospital bed and persons per bed ratio in the United States and each State. Calculations based on the data in this table show that the reported death rate for cancer of the lung is on the average, higher in those states which have a large number of physicians relative to the size of the population then it is in states which have a relatively smaller number of physicians. Likewise, the same death rate is higher in states which have a large number of hospital beds in proportion to the population than it is in states with a relatively low number of beds."

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Source: https://www.industrydocuments.ucsf.edu/docs/gqbl0000

[redacted] OF FINDINGS ON THE INCIDENCE OF LUNG CANCER:

[redacted] The incidence of lung cancer as determined in studies based on clinical, autopsy or death registration material has shown a progressive increase during the past three decades. [redacted] Although the majority of recent workers has held this increase to be real, a number of investigators has cast doubt as to its actuality. Some have criticized the very methods by which the "increase" has been determined. Among other things they contend that at least a part of the increase in lung cancer incidence is due to the lengthened life span, to the increased attention to the disease, and to the frequency and the better diagnosis of hospitalization. Those workers holding the increase in the incidence of lung cancer to be real have based their position largely on the magnitude of this increase in comparison with increases in cancer of other sites.

[redacted]

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Source: https://www.industrydocuments.ucsf.edu/docs/gqbl0000

C H A P T E R I I

RACIAL AND HEREDITARY FACTORS IN LUNG CANCER

2025017831

Source: https://www.industrydocuments.ucsf.edu/docs/gqbl0000

RACIAL ORIGIN AND THE INCIDENCE OF LUNG CANCER:

A few decades ago it was believed that various racial groups are relatively immune to cancer. However, abundant evidence now reported in the literature and cited at length by Fried (1948) and by Poulsen (1949) does not substantiate claims that ethnic derivation is a factor of prime significance in cancer. However, the number of papers that have provided statistical data concerning a possible ethnic factor in bronchiogenic carcinoma are few. Most of such papers have studied the incidence of lung cancer in the Negro and White populations of the United States. The findings of some of these investigations are presented in the following table:

NEGRO-WHITE DISTRIBUTION OF LUNG CANCER CASES IN SOME UNITED STATES HOSPITAL SERIES

Authors & Publication Date	Total No. of Lung Cancers	%age Lung Cancers in Negroes	Source of Data & Remarks N = Negro, W = White
Arkin & Wagner 1936	135	9	Cook County Hosp., Chicago; admissions about 30% Negro.
Rosedale & McKay 1936	57	10.5	Buffalo City Hosp., N:W lung cancer ratio equals N:W ratio in gen. pop. of Buffalo
Stein & Joslin 1938	164	6.1	Hines Hosp., Ill.; no data on rel. admissions rates
Tripoli & Holland 1940	195	33.4	Charity Hosp., New Orleans, 576,810 total admissions, 44.3% Negro
Tripoli & Holland 1940; Halpert, 1941	123	40.7	Male autopsies, Charity Hosp., New Orleans, 5685 total male autopsies, 21.8% Negro.
Fried, 1948	100	32	Johns Hopkins & Baltimore City Hosp. No data on admission or autopsy rates of racial groups

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Source: https://www.industrydocuments.ucsf.edu/docs/gqbl0000

Steiner, 1944	-	43.4	Autopsies, Chicago. (But no. of Negroes autopsied so few that fig. not considered significant).
Ariel et al., 1950	1205	8.5	Males, Hines V.A. Hosp., 1931-1946, Negroes were 8% of all admissions
Gittens & Mihaly 1952	88	87.5	Chronic Chest Service, Harlem Hosp. N.Y.C.; 11.4% W & 1.1% Puerto Rican (Roughly parallel total no. of admissions by age of the 3 races.)

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Source: https://www.industrydocuments.ucsf.edu/docs/gqbl0000

One of the most extensive studies of the incidence of bronchiogenic carcinoma among the Negro population of the United States has been reported from Charity Hospital in New Orleans. At this institution Tripoli and Holland (1940) found that in a period of 20.5 years, 576,810 patients over 12 years of age were admitted. Of these patients, 321,709 were Whites (157,189 male and 164,520 female), and 255,101 Negroes (109,014 male and 146,087 female). Of the 195 cases of pulmonary carcinoma encountered, 130 were in Whites (116 male and 14 female) and 65 in Negroes (55 male and 10 female). These workers concluded that the incidence of lung cancer in White patients at this hospital was more than twice that in Negroes. Ochsner and co-workers (1947) reported parallel observations for this hospital for the 10-year period ending December 31, 1945. The ratio of White to Negro patients was about 2:3 for carcinoma of the stomach and was not significantly different from the admission ratio. In contrast, for carcinoma of the lung this ratio was 2:1. They suggested that a racial factor might be involved in lung cancer in view of this finding and because the increase in incidence of lung cancer appeared primarily among Whites with little change among the Negro patients. Halpert (1941) reviewed the autopsy material of the Charity Hospital. This consisted of 5,685 males (2,610 White and 3,075 Negro) and 3,227 females (1,228 White and 1,999 Negro). Cancer of the lung was found in 81 Whites (73 male and 8 female) and in 54 Negroes (50 males and 4 females.)

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Source: https://www.industrydocuments.ucsf.edu/docs/ggbl0000

Ariel and co-workers (1950) reported that 8.5 percent (102 cases out of 1205) of lung cancer cases in males seen at Hines Veterans Administration Hospital in the period 1931-1946 were Negroes. As Negroes constituted eight percent of all admissions to this hospital during the same period, these workers concluded that there is no racial predilection to or immunity from bronchiogenic carcinoma.

Fried (1948) has stated, that data such as the above should be accepted as demonstrating racial differences only with reservations, because economic, cultural and health conditions (longevity) of the American Negro vary from those of the White. It may be pointed out that data of the United States Bureau of Census does indicate that the longevity of the Negro differs significantly from that of the White.

Brines and Kenning (1937) reported that at the Receiving Hospital, Detroit, Michigan, fifty percent of the cases of primary lung cancer observed were of Central European birth or extraction, but gave no data on the general admission rates of patients of this ethnic background.

Lickint (1935), noting the rarity of cancer including that of the lung in certain primitive peoples recorded by earlier workers expressed the opinion that explanations based on racial factors were unsound and that environmental factors such as diet and smoking habits were more important. Of course, the rarity of lung cancer in primitive races only apparent and native population may be due to the far greater undiagnosed residue

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Source: https://www.industrydocuments.ucsf.edu/docs/gqbl0000

Gittens and Mihaly (1952) reported that though the White to Negro incidence of lung cancer is given in the literature as approximately 2:1, statistical analysis of the records of Harlem Hospital for the five-year period 1945-49 tends to refute that axiom, and to indicate that when all other factors are equalized, the White to Negro incidence is nearly identical.

In conclusion the present reviewer must call attention to the extreme paucity of data bearing on racial origin and incidence of lung cancer that can be accorded any statistical significance. Available evidence fails to demonstrate a racial factor in the etiology of human lung cancer, ~~although such a factor clearly operates in animal strains~~, as Iversen

[redacted]

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Source: https://www.industrydocuments.ucsf.edu/docs/gqbl0000

When Steiner and co-workers (1950) found a great increase in the necropsy incidence of lung cancer in the Los Angeles County Hospital and that the increase was greater than that for cancer in general, they speculated about the cause of this. The racial factor was one of several considerations:

"A small part of the high incidence of lung cancer here reported, but not the increase, may be explained by the inclusion in this series of a number of Mexican women, who exhibit a high incidence of pulmonary carcinoma. This observation, not previously recognized to our knowledge, will be dealt with in detail in a forthcoming monograph on the racial aspects of the tumors in this necropsy population. For present purposes it may be stated that in Mexicans the incidence of lung cancer was as high in women as in men, and that the incidence in the latter equaled that in Caucasoid men. In Negroids, the incidence of lung cancer was approximately the same as in the Caucasoids. Neither the high incidence nor the increase can be attributed to migration of Negroids into the country."

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Source: https://www.industrydocuments.ucsf.edu/docs/gqbl0000

Hueper (1951) commented that when Khanolkar reported on the organ distribution of 3,263 cancers of a Bombay hospital he did not mention lung cancer among the eight types of cancers listed that accounted for 2,652 cancers evaluated. However, until proper standardization as to age and sex has been made, Hueper feels:....

"these observations convey no valid information as to differences in racial susceptibility or special types of exposure to exogenous cancerigenic agents, coinciding with regions populated by different races."

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Source: https://www.industrydocuments.ucsf.edu/docs/gqbl0000

HEREDITARY FACTORS IN LUNG CANCER:

Although some workers have suggested that a hereditary factor might be operating in human lung neoplasms, the evidence for such an assumption is little and not free of ambiguity and criticism. Matz (1938) reported a family history of cancer in 15.2% of his cases of lung cancer, and suggested this is considered only a minimum figure as in many case histories such information had not been sought. Simons (1933)1937) reported a family history of cancer in 64 (6.9 percent out of 930 cases of lung tumors.

Mason (1949) commented that married women appear to be more commonly affected by lung cancer than their single sisters, but did not present any statistical data or case histories.

The observations of Wueper (1942) regarding hereditary factors in the causation of cancer of the respiratory system are worth citing:

> "...Such a reasoning appears far-fetched, considering the fact that approximately 10% of all adults die from cancer of some kind. It does not seem likely that an endogenous factor of a hereditary nature has assumed any important and leading part in the development of the pulmonary cancer trend exhibited during recant decades, especially as this movement is generalized. It is out of the question that the genetic qualities of the population of many peoples in several continents should have undergone uniform fundamental biological changes resulting in a higher inherited susceptibility to pulmonary neoplasia. A hereditary intrinsic factor may have participated in this phenomenon in a passive way; that is, an increase in the number and intensity of external carcinogenic agents may have activated the inherent factor, and thus supported the development of lung cancer at some later period of life... The possibility of such an interrelation is suggested by observations made in mice [redacted]."

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Source: https://www.industrydocuments.ucsf.edu/docs/gqbl0000

In contrast to the findings in human studies, there is abundant evidence of the importance of hereditary factors in the development of pulmonary carcinomas and adenomas in inbred strains of mice. ~~Lung~~ neoplasms in inbred mice ~~usually~~ appear ~~in most inbred strains~~ rarely before the ~~13th~~ thirteenth month and most frequently in the latter half of the second year, when the animal ~~approaches senility~~ has become senile (Greenstein, 1947; Lynch, 1931, 1933, 1935).

The genesis of lung tumors in inbred ~~strains of~~ mice probably depends not only on hereditary predisposition but upon the activation of the cancerous process by the intrinsic or extrinsic environmental factors such as the carcinogenic hydrocarbons. Repeated applications of carcinogenic hydrocarbons or impure tars to the skin (alternated as to site to reduce the incidence of skin tumors) of inbred mice has been demonstrated to increase the incidence of pulmonary tumors (see papers of Andervont, Lynch, Greenstein, Stern and Willheim).

[redacted]

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Source: https://www.industrydocuments.ucsf.edu/docs/gqbl0000

FINDINGS ON RACIAL AND HEREDITARY FACTORS IN LUNG CANCER:

Available evidence fails to demonstrate a racial, familial or other hereditary factor in human lung cancer, although such factors clearly operate in highly imbred animal strains.

Although some evidence of a difference in the incidence of lung cancer between Negroes and Whites in the United States has been reported, it is doubtful that this difference can be explained solely on a racial basis. This difference may be only apparent and due to the larger "undiagnosed residue" and to the smaller life span of the Negro.

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Source: https://www.industrydocuments.ucsf.edu/docs/gqbl0000

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CHAPTER III

~~AGE AND SEX INCIDENCE OF LUNG CANCER~~

Influence of AGE ~~RACIAL~~ AND SEX ~~RELATIONS~~
IN THE INCIDENCE OF LUNG CANCER

2025017842

Source: https://www.industrydocuments.ucsf.edu/docs/gqbl0000

AGE DISTRIBUTION IN THE INCIDENCE OF LUNG CANCER:

A large number of studies have reported primary lung cancer to be a disease of later life, occurring ~~largely during the furth, fifth~~ and sixth decades, and seldom before the age of forty years.

Matz (1938) compiled the following table on the age distribution in ten ~~earlier~~ studies from the period of the 1930's. The data is representative of the findings in other brief studies ~~reported~~ in the literature and not discussed in detail in the present review.

AGE DISTRIBUTION IN THE INCIDENCE OF LUNG CANCER - FROM STUDIES OF THE PERIOD 1929-1937 (after Matz, 1938)

Study:	(A)	(B)	(C)	(D)	(E)	(F)	(G)	(H)	Total
No. of cases:	50	781	295	135	100	46	139	68	1814
Age in yrs.	% age in indicated age group								
Unrecorded	0	2.2	0	0	0	0	0	0	1.2
10-20	0	0	0	0	0	2.2	2.9	0	0.3
20-29	0	6.6	4.1	2.2	4.0	6.5	4.3	1.5	5.2
30-39	4.0	14.2	8.5	6.7	14.0	10.9	12.9	14.7	12.2
40-49	14.0	26.2	17.9	28.9	23.0	13.0	29.5	26.5	24.5
50-59	48.0	30.6	35.6	43.7	32.0	37.0	32.1	39.7	33.6
60-69	24.0	20.2	20.3	16.3	19.0	30.4	15.1	14.7	19.6
70-79	10.0	0	10.2	2.2	8.0	0	2.9	2.9	2.8
80 & over	0	0	3.4	0	0	0	0	0	0.6

(A), Rogers, 1932; (B) Hill, 1934; (C) Olson, 1935; (D) Arkin & Wagner, 1936; (E) Harvey, 1936; (F) Frisell & Knox, 1937; (G) data of Simpson (possibly 1929?) cited by Matz, 1938; (H) Brines & Kenning, 1937. Percentages for the combined series are those of Matz, 1938.

It should be pointed out that the series reported above contain both males and females, and are uncorrected for any possible difference in age distribution associated with sex.

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Source: https://www.industrydocuments.ucsf.edu/docs/gqbl0000

Mason (1949) reported on the age distribution in 1,000 consecutive lung cancers seen at the Northern Regional Chest Surgery Centre in England during the years 1948-1949. As this Centre sees between sixty and seventy percent of all lung cancer diagnosed in the region served, Mason concluded that the data is probably representative of and applicable to the general population. His data is presented in tabular form below:

AGE - SEX DISTRIBUTION IN THE INCIDENCE OF LUNG CANCER IN 1,000 CASES AT NORTHERN REGIONAL CHEST SURGERY CENTRE, ENGLAND, 1948-1949

(adapted from Mason, 1949)

	Percentage in Indicated Age Group		
Age in yrs.	Female (98 cases)	Male (902 cases)	Total (1,000 cases)
10-29	2.0 %	2.2 %	2.2 %
30-39	18.4	8.7	9.6
40-49	33.7	30.6	30.9
50-59	25.5	38.9	37.6
60-69	19.4	18.5	18.6
70 & over	1.0	1.1	1.1

It will be seen from Mason's data that 78.6 percent of the female cases were in the fourth, fifth and sixth decades of life, 88.0 percent of the males, and 87.1 percent of the combined group of 1,000 cases. Whether the finding of a greater percentage of females than males in the age group 30-39 is statistically significant is doubtful, because of the small number of female cases in the study. In the first table in this chapter it will be seen that in the collected data of Matz (1938) 77.9 percent of the lung cancer cases were in the age group 40-69; in contrast Mason's data has 87.1 percent in this group.

Wynder and Graham (1950) have reported the age distribution in 605 males with lung cancer diagnosed in the late 1940's. Their data is presented in tabular form below:

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Source: https://www.industrydocuments.ucsf.edu/docs/gqbl0000

AGE DISTRIBUTION IN 605 MALES WITH LUNG CANCER, ST LOUIS
(Wynder and Graham, 1950)

Age in years	Percentage in Indicated Age Group
30-39	2.3
40-49	17.4
50-59	42.6
60-69	30.9
70-79	6.8
	99.0 %

In this series of Wynder and Graham it will be seen that 70.9 percent of the cases were in the ~~fourth, fifth, and sixth decades of life~~ 50-69 years.

Some authors have recorded the average age and the range of ages in their clinical and autopsy series. A representative collection of such data from the period ~~1930-1950~~ is given in the ~~present~~ following table:

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Source: https://www.industrydocuments.ucsf.edu/docs/gqbl0000

AVERAGE AGE AND RANGE OF AGES REPORTED IN STUDIES OF LUNG CANCER FROM THE PERIOD 1932--1950 (Usually a[illegible])

Author & Date of Publication	Average Age & Std. Dev.	Range in Yrs. (Yng-Old)	No. of cases & Remarks (M= Male)
Rogers, 1932	50.7 yrs.	37 - 77	50 cases
Hill, 1934	51	20's-60's	781 cases
Olson, 1935	53.7	29-89	295 cases (135 M)
Simpson, 1929	54.8	13 - 77	139 cases
Frisell & Knox, 1937	--	21-60's	46 cases
Simons, 1937	54.4 ± 11.7	2.6% < 30	2,796 cases (80% M), collected from lit.
Matz, 1938	45*	21 - 74	138 cases (all M), Vet. Adm. Hospitals*
Menne & Anderson, 1941	55.5	38 - 77	84 cases (78 M)
Ochsner, DeBakey, Dixon, 1947	--	19 - 81	419 cases (86.4% M)
Gibbon, 1949	57	22 - 75	182 consec. cases in 32-month period
Simonds, 1949	57.9 ± 10.8	>30 - ?	82 cases in 4590 autopsies (85% M), 1929-1948
Koelsch, 1950	56	-	~~6165 autopsies~~ Duesseldorf Path. Inst., 1942-'48
Rienhoff, 1950	-	-	Over 50% of 502 cases in 4-6th decades
Ariel et al., 1950	43.2*	-	1205 all male cases at Hines Vet. Adm. Hosp.*
Ariel et al., 1950	48.2*	-	511 male cases as above with histologic proof of lung ca.*

* Authors recognized cases not representative of general population as among all male war veterans in U. S. Vet. Adm. Hospitals.

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Source: https://www.industrydocuments.ucsf.edu/docs/gqbl0000

Inspecting the above table, it will be seen that neglecting the studies based on U.S. male war veterans the average age at onset or diagnosis reported ranges from about 51 to about 58 years.

It should be noted that although primary lung cancer is primarily a disease of latter life, it is seen occasionally in younger persons (see Bibliography of Fried, 1948, Chapter I.) Hauser (1942), Field and Quillian (1943), and Kirsch and Colat (1949, 1950) among other workers have even reported the condition in infants and very young children.

Fulton (1949) found that of 1,610 cases 72.8% were 50 years or over, and 6.6% were under 40; 84.8% were between 40 and 69 years of age.

In a study of operability of lung cancers, Brunner (1951) reported that the average age among his group of 178 cases was 54 years.

Delarue (1951) analyzed 124 cases which were diagnosed in the period 1946-48 and obtained the following age distribution.

AGE INCIDENCE IN 124 CASES OF BRONCHOGENIC CARCINOMA, TORONTO GENERAL HOSPITAL, (CANADA) (Delarue 1951)

Decade	No. of Cases	Peak Incidence
30 to 39	7	
40 to 49	26	
50 to 59	44	56 years
60 to 69	36	
Over 70	11	

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Source: https://www.industrydocuments.ucsf.edu/docs/gqbl0000

McConnell and co-workers (1952) studied occupational and personal factors in lung carcinoma patients in the Liverpool (England) area. From August 1946 to September 1947, 100 cases were seen, and yielded the following data:

AGE AND SEX DISTRIBUTION OF LUNG-CARCINOMA PATIENTS
(McConnell, Gordon and Jones, 1952)

	Age in years				
	30 - 39	40 - 49	50 - 59	60 - 69	Total
Males	8	32	33	20	93
Females	-	1	2	4	7

The authors caution that: "The age-incidence of this series ..... probably does not apply to the disease as a whole, since older patients, obviously unfit for surgical treatment, would not be sent to the thoracic surgical unit which supplied most of our cases."

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RELATION OF SEX TO THE INCIDENCE OF LUNG CANCER:

In Chapter I of this review , it was pointed out that an increase xx in the incidence of lung cancer has been reported. Although this increase has occurred in both sexes, it has been greater in the male than in the female. Probably the most revealing index of this difference in the incidence of lung cancer is the sex ratio (male:female) reported in various studies based on autopsy, clinical, and death registration material, and the increase in the magnitude of this ratio with time. A large number of studies reporting such sex ratios or data from which ratios can be computed xxxx are summarized in the following table which is arranged chronologically according to the date of publication of the cited articles.

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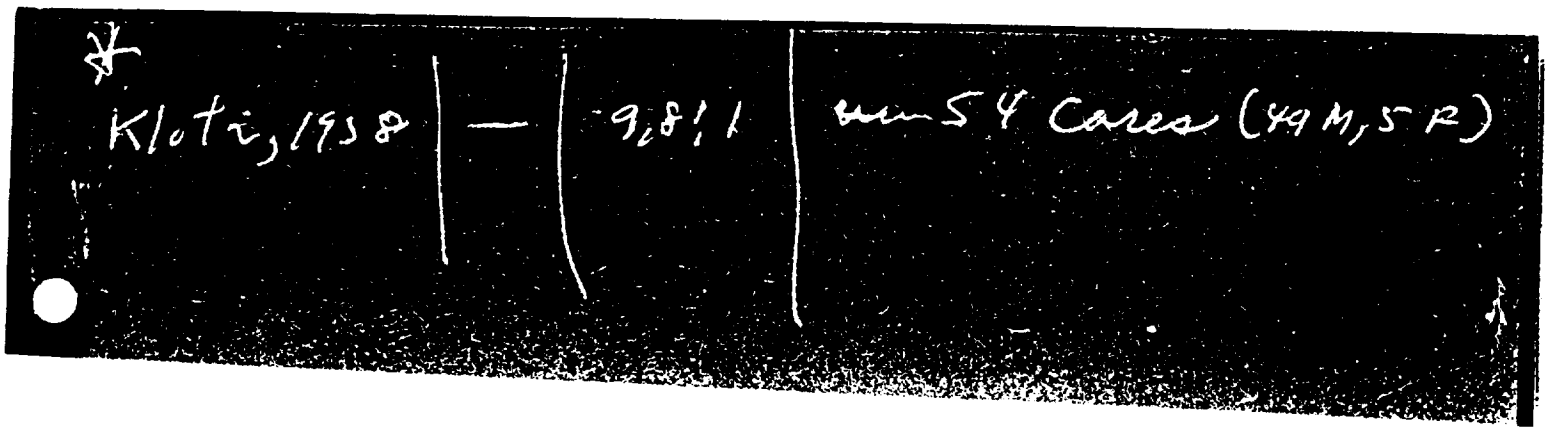

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INFLUENCE OF SEX ON THE INCIDENCE OF LUNG CANCER; SOME SEX RATIOS RECORDED IN THE LITERATURE

Author and Yr. of Publication	Period or Yr.	Male/Female Incidence Ratio	Remarks (M = Male; F = Female)
Junghanns, 1929	1903-'07 1923-'27	2.4:1 4.6:1	Autopsies, Germany; though increase due to more cases in younger men.
Peters, 1932	1908-'13 1917-'22 1927-1931	2.7:1 5.0:1 5.7:1	202 M, 50 F, autopsies, Berlin, Could not confirm Junghanns that increase in younger men.
Lickint, 1935	up to 1935	5.0:1	3,666M, 728 F, autopsy data in recent lit. to 1935.
Lickint, 1935	~~1925-1935~~	—	In Bavaria & Baden in peridd lung cancer increased 26% in F & 31 % in M.
Lickint, 1935	1915-'30	—	Met. Life Ins. policyholders in U.S. increase in all cancer in period 21% in F & 47% in M.
* Simons, 1937 (Notz, 1938)	upto 1937	4:1	5,121 cases collected from literature.
Anon., 1939	1919 1939	ca.5:1 3:1	Met. Life Ins. policyhldrs., death rates for cancer of lung & pleura. In M. death rate for this site increased more rapidly than for malignancies of any other site.
** Ochsner & DeBakey, 1941	up to 1941	3.74:1	Review of 8575 cases in lit.
Dorn, 1943	1938-'42	3:1	Study of hosp. records in 10 U.S. urban areas
Dorn, 1943	1938-'42	3.2:1	Estimation of out of every 100,000 M & F in U.S. at any time 410 M & 340 Males under treatment for cancer, 5 F & 16 M for cancer of lung, every year.
Dorn, 1943	1938-'42	3.67:1	Estimation of out of every 100,00 M & F in U.S. cancer is diagnosed in 220 M and 250 F, cancer of lung in 11 M & 3 F every year.
Clemmesen & Busk 1947	1931 1945	ca. 1.2:1 ca. 3.0:1	Copenhagen, official mortality data. Lung cancer in M increased from 5 to 25 per 100,000, in F from 4 to 7 per 100,000. Data considered stat. signif. as pub. health ins. embraces 85-90% of male pop.

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INFLUENCE OF SEX ON THE INCIDENCE OF LUNG CANCER; SOME SEX RATIOS RECORDED IN THE LITERATURE (Continued)

Author & Yr. of Publication	Period or Yr.	Male/Female Incid. Ratio	Remarks (M = Male; F= Female)
Clemmesen & Busk, 1947	1945	8:1	Centr. Tubercul. Station, Copen-hagen, cases over 45 yrs. of age; only sl. increase in incid. since 1931 and less constant than data for all Copenhagen (see above).
Menne & Anderson, 1941	up to 1941	13:1	78 M, 6 W; consecutive cases.
Ochsner, DeBakey & Dixon, 1947	up to 1947	6.4:1	New Orleans, 356 M, 56 W; consecutive cases.
Lindskog, 1946	1938-'43	1.45:1	100 consecutive cases.
Lindskog & Bloomer, 1948	1947-'48	24:1	Consecutive cases.
Fried, 1948	1936-'48	4.84:1	2,047 cases reported by 10 other workers.
Gibbon, 1949	1947-'49	9:1	182 consecutive cases in period of 32 months.
Simonds, 1949	1929-1948	5.7:1	98 cases in 4590 autopsies but few F; Simonds did not consider figure of statistical value, therefore
Mason, 1949	1948-'49	9.2:1	1,000 cases (98F,902 M) seen at N. Regional Chest Surg. Centre, England.
Kosch, 1950	1942-'48	ca. 5:1	Düsseldorf Path. Instit., 6,155 total autopsies. Crude lung cancer ratio 9:1, but 2:1 preponderance of M in autopsies.
Rienhoff, 1950	up to 1949 or '50	6:1	502 consecutive patients.
Wynder & Graham, 1950	1949-'50	18.5:1	last 150 cases of lung cancer at Barnes Hosp., St. Louis.
Fulton, 1949	1944-1948	7.3:1	1610 cases registered with Liverpool Cancer Control Organization, England.
Delarue, 1952	1946-1948	10.3:1	124 cases diagnosed at Toronto General Hospital, Canada.
McConnell, Gordon & Jones, 1952	1946-1947	13.3:1	100 cases seen in Liverpool [illegible] England and

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Roffo (1939b, 1941a, 1941c) stated that in the observation of 78,000 patients (presumably all with cancer) cancer of the smoking tract (that is, of the mouth, larynx, lung, etc.) ranked first in regard to frequency and that this localization was rarely found in women. He reported (1941a) the following data on the mortality from cancer of the lung and of the larynx according to sex for Buenos Aires in the period 1932-1935.

CANCER MORTALITY ACCORDING TO LOCALIZATION AND SEX IN BUENOS AIRES, 1932-1935 (Roffo, 1941a)
(M = Male, F = Female)

Site	1932 M	1932 F	1933 M	1933 F	1934 M	1934 F	1935 M	1935 F	Totals, 1932-'35 M	Totals, 1932-'35 F	M:F Sex Ratio
Larynx:	115	1	119	5	105	3	126	7	465	16	29:1
Lung :	150	30	187	51	188	48	196	57	721	186	38.8:1

However, as Roffo (1941a) did not present data concerning either the actual number or percentage of men and women dying of all causes, the calculated sex ratios given above ~~are only crude~~.

too much reliance cannot be placed on

Springett (1949) reported data comparing the incidence of cancers of the respiratory tract in England and Wales with that observed in Norway. In Norway, the mortality from cancer of the larynx is about twice as great in men as in women; in contrast in England and Wales about four times greater in men. From the period 1911-1920 to 1935-1939 the mortality from cancer of the lung in England and Wales increases nine times for men, but only fourfold for women. In this that country the mortality from cancer of the lungs has risen for both sexes, and in women it increased from one percent of all cancer deaths twenty-five years previous ago to about three percent

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in 1948-1949.

The Panel on Lung Cancer of the First National Cancer Conference in 1949 reported that there was a wide divergence in the sex incidence of lung cancer noted by various workers. According to this Panel, and as the above tables confirm, sex ratios have been reported in recent years varying from 6:1 up to 25:1. No adequate explanation for this discrepancy was apparent, but in earlier reported series the predominance in men was observed to be much less than it was in more recent studies. This Panel concluded that the finding that the incidence is increasing in both sexes, but apparently much more so in the male, may be due to circumstance that men have been exposed to a greater number of exogenous carcinogenic factors.

Fried (1948) made the following interesting comment:

> "It is to be noted that although there exists a difference in the cancerization of the two sexes as to organ, there is but a slight difference in the total morbidity from cancer between men and women. However, women are affected by cancer at an earlier age period than men. While in men cancer of the lung and of the stomach reaches its peak in the second half of the sixth decade of life (55 to 59), in women, the highest incidence of mammary, cervical and ovarian cancers is in the first half of the fifth decade (40 to 44), i.e., ten to fifteen years earlier. The prevalence of pulmonary cancer in man may possibly be due to the fact that in the female cancer of the genital organs, which occurs with greater frequency at an earlier age, "protects them against the subsequent development of carcinoma of the respiratory organs either by causing death of the patient before the pulmonary neoplasm has had time to develop, or (in case of survival) by creating a virtual "immunity" or resistance to the developemtn of a new

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Kemler and Graham (1950) have recently attempted to ascertain whether the sex preference of lung cancer observed in humans is due to a real biological effect. The technique of Greene was employed involving the heterologous transplantation of human bronchogenic carcinoma into the anterior chamber of guinea pigs' eyes. The female animals employed could be made more 'female' by previous administration of female sex hormones, and similarly, the male animals could be made more 'male' by administration of male sex hormones. In this technique, where a true sex difference in a given cancer exists, the percent of success in transplantation of it to the animal eye varies with the sex of the animal (intensified by administration by the proper sex hormone, if desired). In female guinea pigs, growth occurred in six of twenty-nine attempted transfers and in males in four of twenty-nine attempted transfers. No difference in the growth was observed when testosterone or diethylstilbestrol was administered to these animals. These workers concluded that although it must be granted that the number of animals employed was small, no essential differences were observed in the ability of human bronchogenic carcinoma to grow in the male or female.

In passing, it may be noted that Lynch (1931, 1933, 1935) and Campbell (papers from 1931-1940) concluded from indirect evidence that sex as such has little or no effect upon the incidence of spontaneous and experimental pulmonary tumors in inbred strains of mice. However, Andervont (1935, 1937, 1939) has observed that some carcinogenic hydrocarbons may bring about the development of neoplasms, including those of the lung, more rapidly in male than in female inbred mice and that this activity may persist from one generation to the next.

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Kennaway and Kennaway (1951) reported certain changes in trends in the incidence of cancer of the lung and larynx:

Changes in Mortality from Cancer of Lung and of Larynx, England and Wales (Registrar-General, Statistical Reviews).

	Deaths			
	Cancer of larynx.		Cancer of lung.	
	Men	Women	Men	Women
1921 . . .	641	138	361	186
1929 . . .	831	230	849	359
1949 . . .	813	284	9,327	1,945

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FINDINGS ON ~~THE~~ AGE & SEX INCIDENCE OF LUNG CANCER:

In the previous chapter it was shown that an increase in the incidence of lung cancer has been reported. Although this increase has occurred in both sexes, it has been greater in the male than in the female. The cause for this difference has not been ascertained and certain animal experiments do not support an explanation based solely on sex differences. The fact that the sexes are exposed to widely different environmental situations offers a possible explanation for the observed difference in incidence.

Lung cancer is a disease of later life and seldom develops before the age of forty years.

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C H A P T E R I V

OCCUPATIONAL AND ENVIRONMENTAL FACTORS IN LUNG CANCER

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As Hueper (1942) has observed, the tissues of the respiratory system, second only to the skin, come into contact more often and more intimately with occupational agents of various types present in the air in the form of gases, fumes, vapors, mist, or dust than any other tissue. Further, the lungs are involved in the elimination of many volatile substances entering the body through the skin or other portals.

As the increased mechanization and intensification of industrial production has been most pronounced in the last four or five decades, and as the rise in lung cancer incidence has run somewhat parallel to this development, it has been suggested by many workers that the two phenomena might be etiologically interrelated. However, it is highly questionable according to recorded incidence data that general industrialization per se has etiologic significance in lung cancer. For example, according to Fischer, the lung cancer rate is high in some industrial districts of Germany (Saxony, Rhineland-Westphalia) but low in many highly industrialized regions in Northern Germany.

The possible importance of occupational or other environmental factors (that is, of exogenous or extrinsic factors) in the etiology of human bronchiogenic carcinoma has been given increased emphasis in recent years with the realization that the reported incidence is higher and increasing faster in the male than in the female. Further, the recent findings of Kemler and Graham (1950) and certain animal experiments suggest that the sex preference of lung cancer observed in humans may not be due to a real biological difference (see chapter II).

The following discussion of occupational and environmental factors in the special etiology of lung cancer is not comprehensive. Additional relevant material will be found in the extended and excellent review by Hueper (1942), 1950a, Klotz (1938),

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AIR POLLUTION

~~[illegible] GAS AND COMBUSTION PRODUCTS OF ORGANIC [illegible]~~

The constantly ~~ever~~ increasing use of coal and petroleum products of fuel and the wider use of various petroleum distillates (including tars, creosote and pitch) in a variety of applications ~~has~~ have brought an increasing number of workers in contact with these substances. Both the skin and lung tissues come into intimate contact with these agents, and the contact is not solely occupational for ~~but~~ in industrial centers of the world the general population is exposed to them ~~through~~ to a varying degree, especially through air pollution.

Consideration of the extent of pollution of air in industrial centers ~~from~~ by tar and other aromatic substances is beyond the scope of the present review. No clear ~~or direct~~ and unambiguous study associating the geographical incidence of lung cancer with the atmospheric content of aromatic substances seems to have been made, but several indirect studies ~~bearing on this point~~ are discussed ~~in previous paragraphs~~ in the following pages.

If exposure to oils, tars and combustion products of organic material is of importance in the development of human lung cancers, a great difference might be expected in the death rate from lung cancer in large cities and in rural or suburban communities. Some of these statistical observations bearing on this point are given below. However, they should be considered with caution, and any conclusions should be accepted only with reservation, because the diagnosis of lung cancer is made much more often in major cities because of the better medical facilities and because autopsies are more commonly done in city hospitals rather than in private and rural hospitals ~~and the more frequent employment of autopsies than in rural areas, where, for these reasons, lung cancer is less apt to be diagnosed.~~

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Katz (1927) ~~for example~~, had the impression that town and city dwellers may develop lung cancers more often than ~~x~~ country dwellers. Maternia (1924) and Joannovic (1923) ~~have~~ observed that domestic animals exposed to street dust are more subject to lung cancer than are animals in rural areas. Moise (1921), Maternia (1924), Heilmann (1925), Brandt (1926), Ferency and Matolcsy (1927), Rostoski and co-workers (1926, 1928, 1930), Ewing (1940), and others have implicated the increasing industrial ~~contaminence~~ contaminants as responsible for of city air for the increasing incidence of lung cancer and some of these workers with Staehelin (1925) and Hampelin (1923) have also suggested road dust and the fumes from motor vehicle exhausts. The latter worker has pointed out that Oslo is a city particularly free of dust and ~~shows~~ has a low incidence of lung cancer.

~~In contrast, Konrad and Franke (1929) cited the city of Riga where lung cancer increased without a parallel increase in tarred roads or motor cars.~~ Further, Probst (1927) and Boyd (1930) and Passey and Holmes (1935) observed no higher incidence of lung cancer among chauffeurs or garage workers than in the general populations. Most of Boyd's cases are from country districts of western Canada. Holzer (1925) pointed out that dust has not increased so rapidly as to explain the increased incidence of lung cancer.

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Sucic (1932) reported that in Jugoslavia in a series of 51 cases of lung cancer the percentage incidence of this condition with regard to all cancers increased from ~~6~~ six percent in the period 1923-1925 to ~~18~~ eighteen percent in 1929. This finding in itself was not considered unusual, but important in view of the fact that Jugoslavia is an agricultural country with ~~30~~ thirty percent of its population engaged in farming and related occupations. Sucic concluded that the increase in pulmonary tumors is not confined to the populations of the air-polluted industrial centers of the world.

Simpson (1929) noted a high incidence of lung cancer among workers in the open air, but Bonser (1934) could not agree to this finding since the majority of her ~~workers~~ cases were indoor workers.

Schnurer (1938) analyzed the autopsy observations made on 342 charity patients who had lived in Pittsburgh where the soot content of the air is well known to be extremely high because of the general employment of soft coal as a fuel in ~~the steel and other~~ industrial plants. Schnurer divided the cases into 5 groups according to the degree of pulmonary bituminosis observed, and related the incidence of primary carcinoma of the lung to this classification. Schnurer presented the following table

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BITUMINOSIS AND BRONCHIOGENIC CARCINOMA (SCHNURER, 1938)

Degree of Bituminosis	No. of Cases	Average Age	Primary Lung Cancer
I	30	37.5	-
II	112	42.71	2 (1.8%)
III	146	55.33	3 (2.05%)
IV	46	59.25	5 (10.8%)
V	8	54.12	-

Schnurer (1938) on the basis of the data presented above in view of the ~~jump~~ sudden increase from an incidence of about two percent for primary carcinoma of the lung associated with grade III bituminosis to an incidence of about eleven percent with grade IV suggested a possible causal connection of pulmonary cancer with bituminosis. However, this worker realized that the incidence of primary carcinoma of lung also paralleled the increased average age (see table) and also that the actual number of lung cancer cases involved was small and stated that his conclusion must be accepted with reservations.

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Boyd (1939) pointed out that the increase in the incidence of lung cancer has been world-wide. He stated that pollution of the air with soot and combustion products can hardly be a factor of importance in the increasing incidence of lung cancer seen in the open spaces of Western Canada. According to ~~Turner~~ Boyd, Turner found cancer of the lung as common in Beirut, Syria as in Philadelphia over a period of 10 years, yet most of his patients in that part of the world lived under the same conditions as did their forefathers in the days of the Pharoahs.

Hueper (1942) has stated that data of H. L. Dunn of the U. S. Bureau of Census (apparently unpublished) tabulating the geographic distribution of primary lung cancer in the United States for the period 1930-1934 is suggestive of a causal connection of pulmonary cancer with exposure to soot.

To throw light on soot and other flue products resulting from a combustion of coal and oil as possible etiologic factors in lung cancer, Dorn (1943) calculated hospital admission incidence rates for malignant tumors of the lung and the entire respiratory system for a number of large cities. He found that although air pollution is ~~considered to be~~ great in Pittsburgh, the incidence rate ~~for~~ lung and respiratory cancer in males ~~is~~ lower in Pittsburgh than in Chicago, Detroit, Philadelphia and San Francisco. In ~~the case~~ of females, no ~~real~~ significant difference in the incidence rates for lung and respiratory cancer was detected in the surveyed cities. Dorn concluded that these ~~data~~ do not prove ~~necessarily~~ that atmospheric pollution has no effect upon the incidence of respiratory cancer, but ~~that~~ on the other hand they ~~often no affirmative~~ evidence to the contrary. ~~that such is the case.~~

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Mills (1943) reported that death rates for pneumonia, tuberculosis and respiratory tract and buccal cancer were significantly and sharply higher in the dirtier industrial areas of Cincinnati and Pittsburgh than in the cleaner residential suburbs. This rise was observed to be more striking in the male sex, perhaps because of greater exposure to outdoor polluted air. Mills pointed out that such high rates for pneumonia and tuberculosis in slum areas had been attributed by many workers to poor housing, overcrowding and poor nutrition, but he concluded that the observation that men are much more involved than women raises doubt that these economic factors provide the whole answer. He felt that this doubt was greatly accentuated by the observation that the incidence of buccal and respiratory tract cancer rose as death rates for pneumonia and tuberculosis mounted, probably pointing to long-standing irritation in the respiratory tract as a major factor in the increased incidence of all three diseases in the dirtier urban districts. Mills and Porter (1948) extended the above findings of Mills to include four other major cities. These workers found the death rates for pneumonia, pulmonary tuberculosis and respiratory tract cancer in all the cities studied to bear a direct and significant relationship to the intensity of pollution in the urban atmosphere, and that males were involved much more than females by these effects of pollution. In Chicago, where large population numbers gave stable results, the rise in death rates from pneumonia and tuberculosis from clean to dirty districts was ten times greater for males than for females, and the rise in death rates [illegible] from buccal and respiratory tract

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cancer was more than four times greater.

Mills and Porter (1948) reached the conclusion:

> "The observation that death rates from buccal and respiratory tract cancers rise along with those from pneumonia and tuberculosis points strongly to a general irritation of the tract as the basic factor involved. Economic, housing and nutritional factors appear of much less importance than air pollution, as evidenced by the difference between hazards to males and females."

Mills and Porter (1948) also suggested that the finding that males were more involved than females in the effects of air pollution might be due to the combined and cumulative effects of such pollution in conjunction with the chronic irritative action of tobacco smoking. These workers discussed this possitility at length in a more recent paper (1950), which is described in Chapter VI.

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The Panel on Lung Cancer of the First National Cancer Conference in 1949 reported that no significant difference in the incidence of cancer of the lung has been noted in the admittedly rather inadequate reports ~~appearing~~ comparing the incidence in rural and industrial areas. However, they concluded that more careful analysis of [redacted] comparative incidence from these areas in relation to the size of the population groups should furnish valuable information.

Fulton (1949) surveyed the incidence of lung cancer in a cancer registration program of the Liverpool Cancer Control Organization during the ~~5~~ five-year period 1944-1948. The incidence seemed somewhat higher in industrial areas. Although no statistically significant relation to specific occupations could be demonstrated, painters and furnace men seemed especially prone to lung cancer.

Seelig and Bennignus (1936) exposed 100 mice (Buffalo strain) to soot from bituminous coal and found 21 bronchial hyperplasias and 8 adenocarcinomas of the lung, while only two ~~2~~ cases and one case of these respective conditions developed in ~~50~~ fifty control animals. In subsequent experiments (1938a, 1938b) no lung tumors developed in 100 mice (C57 black strain) after inhalation of 10 percent carcinogenic tar in pine soot. These workers concluded that the coal soot in the earlier experiments was more irritating on account of larger and sharper particles.

Shimkin and Leiter (1940) found sarcomas in about ~~1/2~~ one-half of a group of experimental mice ~~which~~ that had received subcutaneous injections of chimney soot, while intravenous injection caused some increase in lung tumors, but soot from which the tars had been extracted had no effect. Leiter and Shear (1942) injected subcutaneously CH3 strain mice with 50 ~~mg.~~ milligrams of tar extracted by benzene from dust collected in cities, and 30 animals out of 372 surviving animals had sarcomas at the site of injection. Leiter, Shimkin, and Shear (1942) in a further study produced 20 sarcomas among surviving animals

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at the injection site of ~~injected~~ tar extracted by benzene or ether from dust. In contrast, subcutaneous injection of 20 ~~mg.~~ milligrams of non-extracted tar-dust failed to cause sarcomas in a one-year interval. After intravenous injection of the tar extract, no increase in lung tumors was found.

Waller (1949) in a brief report of work in progress stated that benzpyrene had been detected in the dust from nine towns (England) in amounts varying from 0.02 to 0.5 ~~mg.~~ micrograms per cubic meter of air filtered. While differences between the various towns were apparent, it was difficult to assess their significance, as it ~~is~~ was uncertain ~~how far~~ to what extent a sample taken at a given spot ~~is~~ may be representative of ~~that~~ the particular district.

In an air-dust study, reported at the Panel on Lung Cancer of the First National Cancer Conference in 1949, ~~using~~ with dust obtained from several cities in the United States, no significant increase in the incidence of pulmonary mouse tumors could be demonstrated with the dust itself, although a significant increase occurred with an extract. Subcutaneous injection of tar extracted from these dusts induced sarcomas in mice at the site of injection in about ~~8~~ eight percent of the animals.

The extensive literature on chimney soot and various coal tar products as carcinogenic agents in animals and in humans is not subject to review ~~on~~ in the present survey except insofar as it relates directly to the possible etiology of lung cancer. For more extensive bibliography, the reviews of Greenstein (1947), Stern and Willheim (1943), [illegible] should be consulted.

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Lehmann (1930, 1932) presented data on the rapid increase in the use of tar in Germany, and stated that in 1924 only 3,000 tons of tar were used for road surfacing, while in 1929 the yearly consumption had risen to 120,000 tons. The tar used in Germany is usually the hard coal tar obtained from gasworks, and is often mixed with lighter oils. Lehmann found no significant increase in the increase of lung cancer among workers engaged in the tarring of roads in Germany. This worker determined the tar content of air raised from tarred streets (less than 5 percent) and considered the amount too small to make tarring of roads a factor in the ~~special~~ etiology of primary cancer of the lung.

Husted and Piilmann (1935), paralleling the observation of Lehmann, found no significant increase in the incidence of lung cancer among workers employed in road tarring in Denmark, and also found no association of lung cancer incidence with geographical prevalence of tarred roads.

Passey and Holmes (1935) pointed out that the ~~alleged~~ increase in lung cancer in Great Britain appeared prior to the tarring of roads. They further pointed out that if a time factor is required (as is the case in animals), the effect of road tarring on the incidence of primary cancer of the lung should just have been making itself felt in 1935.

Boyd (1939) pointed out that tarring of roads is unlikely as an etiologic agent for lung cancer because the increase was found in Winnepeg in the Province of Manitoba where tarred roads are uncommon.

Kennaway and Kennaway (1947) in a study of the incidence of cancer of the lung and larynx based on data derived from the death certificates of cases of cancer of the lung and of the larynx in males from England

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Brockbank (1950) reported that most of the atmospheric soot in Manchester, England comes from fires and from the exhaust fumes of Diesel engine buses and trucks. A sample of this soot containing 3 percent of a tarry oil produced epithelioma when applied to the skin of mice. However, no evidence could be obtained that inhalation of this tar could produce cancer of the lung as laboratory animals could not be exposed to it for long enough periods of time in their short life span for more than a bronchial irritation to result.

Other studies bearing on air pollution by specific materials are discussed at various points in the following pages.

ROAD TAR AND OIL:

A possible source for the pollution of the air with tars and other aromatic substances considered by many investigators is the dust from tarred or oiled roads. As the tarring and oiling of roads has increased substantially during the same decade in which the incidence of lung cancer has increased, the possibility of an association suggested itself readily.

Brandt (1927) observed that no increase of lung cancer had been observed in France and Sweden in recent years in spite of extensive tarring of roads. Conrad and Franke (1929), on the other hand, reported that pulmonary cancer was on the increase in Latvia, a country in which tarring of roads was not a common practice. Jaffe (1935) made a similar observation and cited the example of Russia where the tarring of roads is [illegible] and automobiles are few in number.

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and Wales for the period 1921-1938 found that a group of open-air occupations where there is exposure to the dust of roads, had incidence somewhat higher than that for the general population. However, drivers of motor vehicles had a normal liability to cancer of the larynx. The incidence of cancer of the lung was not significantly increased for any of these occupations, and in street workers (pavers, masons, concretors and asphalters) there was a distinct decrease in the incidence as compared to the general population. These workers concluded that there was no statistical evidence that tarring of roads had affected the incidence of cancer of the lung. They further concluded that such data as they found available in their own study of the literature suggested that coal tar in the atmosphere, whether derived from roads, chimneys, other sources, did not produce an exceptionally high incidence of cancer of the lung.

Kling and co-workers (1938, 1939) noting the [redacted] observation of Lehmann (1930, 1932) that road dust contained only small amounts of tar was [redacted] a significant etiologic agent in lung cancer, thought this argument spurious and noted that benzpyrene contained in tar adheres to silica particles and could be so inhaled. They felt that this possibility might in part explain the rise in lung cancer in [redacted] France during the 1930's.

[redacted]

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Kawahata (1938) and Kuroda and Kawahata (1938) reported a high incidence of lung cancer among stokers of Japanese generator gas plants exposed to inhalation of hot tar fumes.

Hueper (1942) concluded that as no systematic and reliable study on the incidence of lung cancer in persons coming in contact with tarred roads has been made, definite conclusions on the possible carcinogenic importance of tar contained in road dust must be deferred.

Dungal (1950) has reported that in Iceland lung cancer is still a rare disease, the incidence being similar to that seen in many European countries at the beginning of the century. In Reykjavik, the capital of Iceland, tarring of the streets began about 1920, and since then most of the streets have been tarred. Dungal concluded that if the tarring of roads had anything to do with the increased incidence of lung carcinoma, a greater rise in lung cancer should have been seen.

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Freedman (1950) observed that it is well known (see Ross, 1948) that the 3,4-benzpyrene content of tars varies with their origin. British and Belgium tars have a high benzpyrene content and are derived from the high temperature distillation of petroleum oils and from gas works; in contrast, the French and American tars are low in benzpyrene content and are derived from low temperature distillation or from bitumine or asphalt. Freedman concluded that this observation should be taken into account in any discussion of tarred roads or atmospheric pollution as etiologic factor in cancer.

In passing, it may be noted that Campbell (1934a, 1934c, 1943a) observed the prolonged exposure of mice to dust collected from tarred roads and containing two percent tar caused skin cancer when painted and greatly increased the incidence of primary lung tumors when inhaled. At least twenty percent of the tumors on examination proved to be of the malignant type. When most of the tar was extracted, the residual tar did not give rise to skin tumors, but did cause an increase of lung tumors (see Campbell, 1937). This latter finding was in agreement with Campbell's later experiments (1940) that inhalation of silica or ferric oxide provoked an increase in the incidence of lung tumors. Leitner and Leitner and Shear (1942), Shimkin and Shear (1942) confirmed in general the findings of Campbell employing tar extracted from city dust. However, other workers in parallel experiments have obtained less positive results. Space does not permit consideration of the vast literature on the effects of tar upon the development of the incidence of experimental tumors in animals. The reviews of Brockbank (1932), Mueper (1942), Stern and Willheim (1950), and Greenstein (1947) should be consulted.

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COAL DUST:

Chronic exposure to coal dust has been suggested directly or indirectly by some workers as a possible factor in the genesis of the pulmonary cancers. However, existing evidence does not support this view.

Kennaway and Kennaway (1936, 1947) reported that the incidence of pulmonary and laryngeal neoplasms is actually lower in coal miners than in the general population of England. Further, Allen (1934) concluded that the incidence of pulmonary cancer among the Pennsylvania coal miners was no greater than in the general population of that state.

Campbell (1944) exposed mice and guinea pigs to airborne coal dust for periods up to three to four years. In mice with anthracite dust no increase in pulmonary tumor incidence was observed, and with bituminous coal dust only a slight increase in lung tumor incidence ~~xxxxxxxxxxx~~, but only a borderline significance was observed. In guinea pigs with anthracite dust, no lung tumors were observed, and adenomatous hyperplasia of the bronchial epithelium was obtained in one case only.

The possible carcinogenic action of the combustion products of coal including chimney soot is considered elsewhere in the present chapter, especially in the section on "[illegible] Air Pollution",

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AIR-BORNE PETROLEUM OILS:

A few workers have suggested that occupational exposure to air-borne petroleum oils may be an etiologic factor in the development of pulmonary tumors. Kennaway and Kennaway (1936, 1947) observed a higher incidence of laryngeal cancer in mule-spinners, who inhale carcinogenic shale oils as a mist thrown off from the lubricated spindles, than in the general population. Southham (1928) reported parallel findings. Huguenin and co-workers (1949) have also associated occupational exposure to nebulized industrial oils with selected cases of lung cancer and have suggested the need of further study of this association. The development of granulomas with accompanying induration of the lung has been occasionally reported following occupational inhalation of air-borne paraffin or use of medicaments containing liquid petrolatum in the therapy of respiratory difficulties. Wood (1943) has recorded an unique case of a bilateral carcinoma of the lung in a patient with lipoid pneumonia caused by inhalation of mineral oil as a mist. The reviews of Hueper (1942, 1950[a]) should be consulted for further relevant bibliography.

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COMBUSTION PRODUCTS OF PETROLEUM [redacted]:

A large number of investigators have suggested the combustion products of petroleum products especially the exhaust fumes of internal combustion and diesel engines in the etiology of pulmonary tumors. This alleged relationship has been attractive because of the parallelism between the increase in automobile traffic and the increase in the incidence of lung cancer (Heilmann, 1925; Duguid, 1927; Ferenczy and Matolcsy, 1927; and Lorentz, 1930; etc.). However, the existence of such a relationship has been ~~seriously~~ questioned by many other workers. Some of the statistical evidence speaking against this relationship has already been discussed under the heading [redacted] "Air Pollution". Lehmann (1930, 1932) [redacted] reasoned that if a relationship does exist between the extent of auto traffic and the incidence of lung cancer, the relative incidence of lung cancer in different countries should be correlated numerically to the number of automobiles and the number of inhabitants. Using the data available for the United States and Germany, he could find no such correlation.

Kennaway and Kennaway (1947) in a study of death certificates of cancer of the lung and of the larynx in males from England and Wales for the period 1921-1938 reported that workers exposed to coal gas and tar tend to show an increased prevalence of cancer of the lung, but in the period 1933-1938 the incidence did not exceed 2.5 times that of the general population.

Ochsner, according to Laurence (1940), stated that it is unlikely that motor exhaust fumes are the factor accounting for the increased incidence of lung cancer. A check on automobile sales during the period 1926-1936 showed that in the United States while there was a rise in such sales up to 1929, the sales showed a distinct drop following the stock market crash while the incidence of lung cancer continued to show a steady rise.

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As discussed at length in ~~other~~ earlier portions of this review, the incidence of lung cancer has often increased in rural areas and areas where the use of automobiles is extremely limited as ~~greatly~~ much as it has ~~increased~~ in industrial and urban areas. Additional material on the role of combustion products is to be found under "General air Pollution".

In passing, it may be briefly noted that some workers have produced occasionally tumor-like structures of the bronchial mucosa by exposure of mice and guinea pigs to motor exhaust fumes. (See literature cited by Brockbank, 1932, and Hueper 1942, 1950). In contrast, Smith (1928) by exposing animals to pitch fumes, products of an internal combustion engine, or by painting the skin with gasoline, was unable to produce pulmonary tumors in mice. Campbell (1936, 1939) exposed mice for seven hours on five days of the week during most of their lives to exhaust gases from internal combustion engines at concentrations resembling those observed in garages in city blocks. Carbon (soot) and lead were excluded. Such exposure had no significant effect on the incidence of lung tumors in the mice.

Klotz (1938) and Hueper (1942) after review of the literature concluded that there is no direct evidence to connect cancer of the lung in humans with fumes from gasoline engines and that such indirect evidence existing is far from convincing.

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EXPOSURE TO RADIATIONS AND CERTAIN MINE DUSTS

Pulmonary tumors in ~~miners employed in mines in which the~~ workers mining ores that are radioactive (uranium) and that contain arsenic and cobalt as well (Schneeberg and Joachimsthal in particular) have been recognized clinically for at least seventy years. The clinical picture of such lung tumors is often initially that of pneumonoconiosis (chronic lung inflammation due to dust), and the onset of symptoms may be delayed for years after the patient has ceased to engage in mining. The recent incidence of such lung tumors in miners at the above-mentioned mines has been estimated to ~~be higher than~~ as high as fifty percent (Spencer, 1950). The panel on lung cancer of the First National Cancer Conference in 1949 [illegible] concluded that there is insufficient evidence that such tumors are due solely to irradiation with alpha rays emitted from the radon present in the air. Arsenic and cobalt are also present in the dust of these mines and may be responsible in part for the high incidence of lung cancer. Analysis of autopsied lung tissue proved negative for radioactivity or significant chemicals, but Pirchan and Sikl (1932) held this finding did not rule out chemical factors that might be rapidly removed from the living. The extensive literature on pulmonary tumors among these miners and among radium workers has been extensively reviewed by Schmorl (1922-1923), by Hueper (1942), and by Fried (1950a) and by Lorenz (1944) and is not subject to further review in the present survey.

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Lickint pointed out that chronic bronchitis may be an important phase in the pre-cancerous phase of the development of some lung tumors. He observed that the male:female ratio for chronic bronchitis increased from 307:198 (or 1.50:1) in the period 1915-1925 to 339:148 (2.4:1) for 1926-1931.

Matz (1938) reported that 81 of 160 cases of lung cancer in men gave a history of one or more diseases of the respiratory tract that cause irritation of the bronchial mucosa with possible proliferation of the lining cells and resulting metaplasia. The diseases most frequently reported were influenza, bronchitis, pneumonia, pleurisy, pulmonary tuberculosis, bronchial asthma, and the residuals of warfare gassing. Matz concluded that the incidence of these diseases is sufficiently great to be suggestive that such conditions constitute a factor in the inception of bronchiogenic carcinoma.

Menne and Anderson (1941) restated the conclusion of earlier workers concerning the possible influence of prolonged and severe respiratory infections and concluded that any continuous respiratory irritant or infection producing repeated denuding with re-epithelialization of the bronchial mucosa might aid in the establishment of a malignant pattern.

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Campbell caused mice to inhale pitchblende dust containing no arsenic and almost no radium over a period of time, and obtained only inconclusive results regarding an increased incidence of lung tumors in the experimental animals. Lorenz, Heston and co-workers (1946) exposed mice to gamma rays (8.8 roentgens per 8 hours), and observed a significant increase in the incidence of pulmonary tumors as compared to control mice of the same strain. It was reported that the Lung Cancer Panel of the First National Cancer Conference in 1949 that whole-body continuous exposure to gamma radiation to a total dose of about 2400 roentgens proved to be a weak carcinogenic agent in strain A mice. Henshaw and co-workers (1946) have reported that mice exposed to atomic pile radiation (fast and slow neutrons, gamma rays) develop neoplasms at a far greater rate than control animals. Other workers have shown that ultra-violet irradiation sufficient to produce skin tumors does not increase the incidence of pulmonary tumors in mice, suggesting that no carcinogen is formed in the skin and subcutaneous tissue. Other studies on the induction of tumors in animals exposed to radiant energy have been reviewed at length by Hueper (1942, 1950)[6], and are not subject to further review in the present survey. It may be noted that no cases have been reported suggesting the induction of human bronchiogenic carcinomas by exposure to X-rays at diagnostic or even at therapeutic dosage rates.

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